

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LPB/P102676WO		FOR FURTHER ACTION		See Form PCT/PEAA16
International application No. PCT/GB2004/004054		International filing date (day/month/year) 23.09.2004		Priority date (day/month/year) 23.09.2003
International Patent Classification (IPC) or national classification and IPC C12N15/85, C12N5/10, A01K67/027, C12N9/16, C07K14/59, C12N9/18, G01N33/50, A61K49/00				
Applicant CXR BIOSCIENCES LIMITED et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 12 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 1 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 21.07.2005		Date of completion of this report 20.01.2006		
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized Officer Brouns, G Telephone No. +31 70 340-3789 		

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**INTERNATIONAL PRELIMINARY REPORT
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Box No. 1 Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-31 as originally filed

Claims, Numbers

10-33 as originally filed
1-9 received on 25.07.2005 with letter of 21.07.2005

Drawings, Sheets

1/5-5/5 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 1-8, 15, 19-30 (all partially); 16-18, 31-33 (complete)

because:

- ☒ the said international application, or the said claims Nos. 31-33 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
☒ no international search report has been established for the said claims Nos. 1-8, 15, 19-33 (all partially); 16-18 (complete)

- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- ☐ has not been furnished
☐ does not comply with the standard

the computer readable form

- ☐ has not been furnished
☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

- ☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☒ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-8,15,19-33 (all partially); 9-14 (all complete) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	10-14,21-25,28-33
	No: Claims	1-9,15,19,20,26,27
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-15,19-33
Industrial applicability (IA)	Yes: Claims	1-15,19-30
	No: Claims	31-33(?)

2. Citations and explanations (Rule 70.7):

see separate sheet

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed
 - ☐ filed together with the international application in computer readable form
 - ☒ furnished subsequently to this Authority for the purposes of search and/or examination
 - ☒ received by this Authority as an amendment on
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional observations, if necessary:

The present application relates to the use of secretable or excretable proteins as reporter proteins in cell lines or transgenic non-human animals, preferably proteins that are secreted in the urine of said transgenic non-human animal.

Re Item I

Basis of the report

1) Claims 1-9 have been filed on 21.07.2005 under Article 34(2)(b) PCT, and claims 10-33 are as originally filed, but are considered to refer back to amended claims 1-9. The new claims do not appear to introduce new subject-matter.

2) Reference is made to the following documents:

- D1: WO 00/79264 A (TSAI TING FEN ; BAYLOR COLLEGE MEDICINE (US); ZOGHBI HUDA Y (US); CHEN) 28 December 2000 (2000-12-28)
- D2: JAIN RENU K ET AL: "Aggregation chaperones enhance aggregation and storage of secretory proteins in endocrine cells" J. BIOL. CHEM., vol. 275, no. 35, 1 September 2000 (2000-09-01), pages 27032-27036
- D3: WANG MANPING ET AL: "MUSEAP, a novel reporter gene for the study of long-term gene expression in immunocompetent mice" GENE (AMSTERDAM), vol. 279, no. 1, 14 November 2001 (2001-11-14), pages 99-108
- D4: BAO RUDI ET AL: "Activation of cancer-specific gene expression by the survivin promoter." J. NATL. CANC. INST., vol. 94, no. 7, 3 April 2002 (2002-04-03), pages 522-528
- D5: DEY ANUP ET AL: "Tissue- and cell type-specific expression of cytochrome P450 1A1 and cytochrome P450 1A2 mRNA in the mouse localized in situ hybridization" BIOCHEM. PHARMACOL., vol. 58, no. 3, 1 August 1999 (1999-08-01), pages 525-537
- D6: MATZUK MARTIN M ET AL: "Overexpression of human chorionic gonadotropin causes multiple reproductive defects in transgenic mice." BIOLOGY OF REPRODUCTION, vol. 69, no. 1, July 2003 (2003-07), pages 338-346
- D7: COLE LAURENCE A: "Immunoassay of human chorionic gonadotropin, its free subunits, and metabolites" CLINICAL CHEMISTRY, AMERICAN ASSOCIATION FOR CLINICAL CHEMISTRY. WINSTON, US, vol. 43, no. 12, December 1997 (1997-12), pages 2233-2243
- D8: RULLI SUSANA B ET AL: "Reproductive disturbances, pituitary lactotrope adenomas,

and mammary gland tumors in transgenic female mice producing high levels of human chorionic gonadotropin" ENDOCRINOLOGY, vol. 143, no. 10, October 2002 (2002-10), pages 4084-4095

D9: HERMEKING H ET AL: "14-3-3 sigma is a p53-regulated inhibitor of G2/M progression" MOLECULAR CELL, CELL PRESS, CAMBRIDGE, MA, US, vol. 1, December 1997 (1997-12), pages 3-11

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3.1) In view of non-unity (see Item IV below), no search report has been established for the subject-matter of claims 1-8, 15, 19-33 (in part) and claims 16-18 (complete).

No opinion is given for said unsearched subject-matter.

3.2) Claims 31-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

4) The common concept linking together the nucleic acid sequences, cells, transgenic animals and uses thereof of the present set of claims, is that they relate to reporter proteins that are secreted or excreted, further comprising a peptide tag for detection.

This common concept is not novel, see for instance document D1 (page 16, lines 18-page 17, line 10), which discloses the use of reporter proteins with a peptide tag that are secreted into biological fluids and tissues, for instance blood and urine.

Because the use of secretable or excretable reporter proteins further comprising a peptide tag was known in the art before the priority date of the present application, the following groups of inventions are not so related as to form a single general inventive concept and therefore do not fulfil the requirement for unity of invention referred to in Rule 13 PCT:

**INTERNATIONAL PRELIMINARY
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(SEPARATE SHEET)**

International application No.

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Invention 1: use of secreted embryonic alkaline phosphatase (SEAP) further comprising a peptide tag as a secretable or excretable reporter gene (claims 1-8, 15, 19-33 (all partially); claims 9, 10 (complete))

Invention 2: use of human beta choriogonadotropine (β -hCG) further comprising a peptide tag as a secretable or excretable reporter gene (claims 1-8, 15, 19-33 (all partially); claims 11-14 (complete))

Invention 3: use of follicle stimulating hormone further comprising a peptide tag as a secretable or excretable reporter gene (claims 1-8, 15, 19-33 (all partially); claim 16 (complete))

Invention 4: use of antibody gamma or light chain (Bence Jones) protein further comprising a peptide tag as a secretable or excretable reporter gene (claims 1-8, 19-33 (all partially); claim 17 (complete))

Invention 5: use of feline urinary protein further comprising a peptide tag as a secretable or excretable reporter gene (claims 1-8, 19-33 (all partially); claim 18 (complete))

Inventions 1 and 2 (claims 1-8, 15, 19-33 (all partially); claims 9-14 (complete)) relating to SEAP and β -hCG as reporter proteins have been the subject of the International Search Report and this report refers only to subject-matter relating to said two inventions.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INVENTION 1

NOVELTY (Article 33(2) PCT)

5) D2 discloses an SEAP nucleic acid encoding SEAP and a peptide tag, and said tagged SEAP is secreted from cells transfected with said nucleic acid (D2, abstract; page 27032, right-hand column, experimental procedures; table 1).

In view of the above, the subject-matter of claims 1-9, 15, 19, 20, 26 and 27, relating to nucleic acid sequences encoding SEAP and a peptide tag as well as host cells comprising said nucleic acid sequence, is not novel.

The subject-matter of claims 10, 21-25 and 28-33 is not disclosed in the prior art, therefore said claims are novel (Article 33(2) PCT).

INVENTIVE STEP (Article 33(3) PCT)

6.1) Document **D3** relates to SEAP and indicates its suitability as a reporter protein in transgenic animals for studying promoters, as well the influence of metabolic, developmental and environmental signals on gene expression *in vivo* (D3, page 107, last paragraph). From this the subject-matter of claim 21 differs in that the SEAP reporter protein further comprises a peptide tag.

The problem to be solved by the present invention may therefore be regarded as the provision of a further non-human animal expressing SEAP as a reporter protein.

The solution proposed in claim 21 of the present application cannot be considered as involving an inventive step, since no surprising effect has been demonstrated for SEAP further comprising a peptide tag. The transgenic non-human animal of examples 1 and 2 of the present application expresses untagged SEAP, and in view of page 19, lines 26-28 of the description, it seems that the presence of a peptide tag is not essential to practise the present invention.

The addition of a peptide tag for detection of a protein is a routine option for the skilled person, hence no inventive step may be acknowledged for the non-human transgenic animal/mammal of claims 21 and 22, or uses thereof as indicated in claims 31-33 (D3, page 107, last paragraph).

6.2) **D4** discloses the use of SEAP reporter protein to study the activity of the survivin gene promoter in transformed cell lines and it is indicated that said reporter gene system is suitable for monitoring tumor initiation and progression in tumor prone transgenic animals (D4, page 528, last paragraph). Since no effect of a peptide tag linked to the SEAP reporter protein has been demonstrated in the application, and since untagged SEAP reporter protein seems to be suitable to practise the present invention (description page 19, lines 26-28), no inventive step may be acknowledged for the use of a nucleic acid construct encoding SEAP reporter protein and further a peptide tag for the detection of a gene activation event (claims 29, 30), method of detecting a gene activation event (claim 31), or a method for screening and characterising for infections or diseases (claim 33).

6.3) Dependent claims 10, 23-25 and 28 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, the reasons being as follows:

The skilled person is aware of a large number of promoters, for constitutive, inducible or tissue specific expression. No surprising effect has been indicated for the selection of the Cyp1A1 promoter (claim 10) known from D5 to be expressed in epithelium lining the gastro-intestinal tract, the renal corpuscle and urinary epithelium of the renal calyx, ureter and bladder.

The use of a secretable reporter gene further comprising a peptide tag to analyse expression in different tissues, specifically blood and urine is known, for instance from D1 (page 16, line 18-page 17, line 10). Furthermore, tissue specific expression is a function of a promoter and the present application does not indicate which technical features are required to obtain reporter protein expression in the various tissues of claims 24 and 25. The combination of two different reporter proteins is suggested in D1 (page 13, lines 16-21) and no special effect has been indicated for the use of more than one reporter system in a host cell, cell line or non-human transgenic animal in the application (claim 28).

6.4) In conclusion, no inventive step has been acknowledged for claims 1-10, 15 and 19-33 when restricted to SEAP (Article 33(3) PCT).

INVENTION 2

NOVELTY (Article 33(2) PCT)

7) D6 discloses a transgenic mouse expressing β -hCG under transcriptional control of the metallothionein promoter. It is indicated that in a mouse expressing both α - and β -hCG the product encoded by the transgenes is detected in the urine. Since it is known that secreted, free β -hCG may be found in blood and urine (D7, fig. 1), it is considered that the single β -hCG transgenic mouse of D6 will secrete β -hCG in the urine.

In addition, D8 discloses a transgenic mouse comprising a nucleic acid construct encoding secretory β -hCG (D8, fig. 1A; paragraph bridging pages 4089 and 4092)

D6-D8 do not disclose a nucleic acid encoding β -hCG 'further comprising a peptide tag', therefore the subject-matter of claims 1-8, 11-14 and 19-33 restricted to β -hCG are novel (Article 33(2) PCT).

INVENTIVE STEP (Article 33(3) PCT)

8.1) Claim 11 relates to a 'modified' β -hCG, but does not indicate which modification is essential to practise the invention. The description discloses a wild-type β -hCG with an internal epitope tag. There is no indication that this modification would alter the characteristics of β -hCG, therefore wild type β -hCG is considered to be suitable to practise the present invention.

D6 discloses a nucleic acid construct encoding β -hCG (D6, fig. 1A), which is considered to be intrinsically 'secretable' and 'excretable'. From this the subject-matter of claim 1 differs in that the construct further encodes a peptide tag for detection of β -hCG.

The problem to be solved by the present invention may therefore be regarded as the provision of a further nucleic acid encoding β -hCG.

The addition of a peptide tag as additional means for detection of a heterologous reporter protein is explicitly suggested (D1, page 17, lines 4-6).

D6 discloses host cells and transgenic mice comprising the aforementioned nucleic acid construct, therefore independent claims 19-21 lack inventive step for the same reasons as set out for claim 1.

8.2) The use of secretable/excretable reporter genes in xenotransplant models as a biological reporter system that permits non-invasive measurement of biochemical changes is known from **D4** and it is indicated that said system may be used for screening for cancer (D4, page 528, last sentence). The subject-matter of claims 29-33, when restricted to invention 2, relates to the arbitrary selection of a further reporter gene for use in a xenotransplantation model, namely β -hCG, from a large range of reporter genes from which the skilled person may choose, and for which no surprising technical effect has been indicated in the application. The use of the stratifin promoter in combination with a reporter protein (claim 12) is known from D9 (fig. 3). Providing a peptide tag to the reporter protein solves an independent problem, namely detection of a heterologous protein, and this solution is obvious to the skilled person (D1, page 17, lines 4-6).

8.3) Dependent claims 2-8, 15, 22-28 and 30 do not contain additional technical features that render the subject-matter of independent claims 1, 19-21, 29 and 31-33 inventive: The functional definitions of claims 2-8 and 24-27 do not allow distinction between β -hCG of the present application and β -hCG known in the art.

Non-human transgenic animals are known to include mammals and mice (claims 22, 23)

No special effect has been indicated for the use of more than one reporter system in a host cell, cell line or non-human transgenic animal (claim 28), which is known from D1 (page 13, lines 16-20).

8.4) In conclusion, no inventive step has been acknowledged for the subject-matter of claims 1-8, 11-13, 15 and 19-33, when restricted to β -hCG.

8.5) The selection of the β -hCG reporter protein, in combination with the stratifin promoter and a myc epitope tag for use in methods of detecting gene activation or screening for toxicologically induced stress or diseases has not been suggested in the art (claim 14). Subject-matter restricted to this specific combination appears inventive (Article 33(3) PCT).

INVENTIONS 1 AND 2

INDUSTRIAL APPLICABILITY (Article 33(4) PCT)

9) For the assessment of the present claims 31-33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

10) The present set of claims comprises a number of functional definitions (for instance the nucleic acid encoding a reporter gene of claims 1-10 that 'is secretable/excretable', 'is produced by...', 'is increased by...', 'is a result of..') that lack technical features that define the subject-matter for which protection is sought (Article 6 PCT).

Claims

1. A nucleic acid construct comprising a nucleic acid sequence comprising a reporter gene encoding a reporter protein that is secretable as a protein or product from a cell where it is expressed or produced and that is excretable from a whole animal the construct further comprising a peptide tag.
2. A nucleic acid construct according to claim 1 wherein the secretable/excretable protein or product is produced by modulated gene transcription.
3. A nucleic acid construct according to claim 1 wherein the secretable/excretable protein or product is produced by increased reporter translation.
4. A nucleic acid construct according to claim 3 wherein the increased reporter translation is as a result of increased stability or decreased turnover of mRNA.
5. A nucleic acid construct according to claim 1 wherein the secretable/excretable protein or product is produced by post-translational modulation.
6. A nucleic acid construct according to claim 5 wherein the post-translational modulation is increased reporter stability through removal of polyubiquination or as the result of accumulation or excretion of small molecule metabolites.
7. A nucleic acid construct according to any preceding claim further wherein the peptide tag is in the form of an epitope tag.
8. A nucleic acid construct according to any preceding claims additionally comprising a promoter element upstream of the (i) a nucleic acid sequence encoding a secreted/excreted protein, and/or (ii) a nucleic acid sequence encoding a peptide tag.
9. A nucleic acid construct according to any preceding claim wherein the secreted/excreted reporter protein is SEAP.

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